

WHAT IS CLAIMED IS:

1. An activated polymer derivative, said polymer derivative comprising one or more first water soluble, non-peptidic polymeric segments having at least about 200 repeating units covalently attached through at least one linkage moiety to at least one second water soluble, non-peptidic polymeric segment having no more than about 120 repeating units, wherein said units of said first and second polymeric segments may be the same or different, wherein said at least one linkage moiety does not substantially alter the properties of said polymer derivative, said polymeric derivative having at least one active moiety selected from the group consisting of electrophilic moieties and nucleophilic moieties located on one of said first and second polymeric segments.
2. The polymer derivative of Claim 1 wherein said at least one active moiety is a single moiety located on said second polymeric segment.
3. The polymer derivative of Claim 1 wherein said first polymer segment further comprises a protected functional group.
4. The polymer derivative of Claim 1, wherein the first and second polymeric segments are independently selected from the group consisting of poly(alkylene glycol), poly(olefinic alcohol), poly(vinylpyrrolidone), poly(hydroxyalkylmethacrylamide), poly(hydroxyalkylmethacrylate), poly(saccharides), poly( $\alpha$ -hydroxy acid), poly(vinyl alcohol), polyphosphazene, polyoxazoline, poly(N-acryloylmorpholine), and copolymers, terpolymers, and mixtures thereof.
5. The polymer derivative of Claim 1, wherein said first polymeric segment has from about 200 to 2000 repeat monomer units.
6. The polymer derivative of Claim 4, wherein said first polymeric segment has from about 200 to 700 repeating units.
7. The polymer derivative of Claim 1, wherein said second polymeric segment has from 1 to about 120 repeating units.

8. The polymer derivative of Claim 1, wherein said second polymeric segment has from about 40 to 80 repeating units

9. The polymer derivative of Claim 1, wherein said first and second polymeric segments are poly(ethylene glycol).

5 10. The polymer derivative of Claim 1, wherein said linkage moiety between said first and second polymeric segments is a hydrophilic moiety selected from an amide or carbamate linkage.

10 11. The polymer derivative of Claim 1, wherein said active moiety is selected from the group consisting of hydroxyl, protected hydroxyl, active ester, active carbonate, acetal, aldehyde, aldehyde hydrates, alkenyl, acrylate, methacrylate, acrylamide, active sulfone, amine, protected amine, hydrazide, protected hydrazide, thiol, protected thiol, carboxylic acid, protected carboxylic acid, isocyanate, isothiocyanate, maleimide, vinylsulfone, dithiopyridine, vinylpyridine, iodoacetamide, epoxide, glyoxals, diones, mesylates, tosylates, thiosulfonate, and tresylate.

15 12. The polymer derivative of Claim 1 wherein said polymeric segments are selected from the group consisting of linear, branched, and multiarmed polymeric segments.

20 13. An activated polymer derivative, said polymer derivative comprising a linear monomethoxy poly(ethylene glycol) segment having from about 200 to 700 repeating monomer units covalently attached through at least one amide or carbamate linkage moiety to one terminus of a linear poly(ethylene glycol) segment having from 1 to 120 repeating monomer units, and wherein said poly(ethylene glycol) segment of 1 to 120 repeating monomer units includes at least one active moiety selected from the group consisting of electrophilic moieties and nucleophilic moieties at the terminus thereof  
25 opposite said poly(ethylene glycol) segment of 200 to 700 repeating monomer units.

14. A polymer derivative selected from the group consisting of monomethoxy poly(ethylene glycol)-p-toluenethiosulfonate; monomethoxy poly(ethylene glycol)-propionic acid; monomethoxy poly(ethylene glycol)-propionic acid, N-

hydroxysuccinimide ester; monomethoxy poly(ethylene glycol)-propionic acid, methyl ester; monomethoxy poly(ethylene glycol)-butanoic acid; monomethoxy poly(ethylene glycol)-butanoic acid, N-hydroxysuccinimide ester; monomethoxy poly(ethylene glycol)-butanoic acid, methyl ester; monomethoxy poly(ethylene glycol)-amine; monomethoxy poly(ethylene glycol)-propionaldehyde; monomethoxy poly(ethylene glycol)-propionaldehyde, diethyl acetal; di-monomethoxy poly(ethylene glycol)-lysine propionaldehyde; di-monomethoxy poly(ethylene glycol)-lysine propionaldehyde, diethyl ester; and monomethoxy poly(ethylene glycol)-maleimide; wherein said polymer derivative has a molecular weight of at least about 10,000 Daltons and has at least two distinct poly(ethylene glycol) segments attached by a linking group.

15. The polymer derivative of Claim 14 conjugated to a biologically active molecule.

16. The polymer derivative of Claim 1 having the structure (Poly)<sub>a</sub>-X-(Poly)<sub>b</sub>-Y, wherein (Poly)<sub>a</sub> is a water-soluble, non-peptidic polymeric segment having more than about 200 repeating units, X is a linking moiety that does not substantially alter the properties of the polymer derivative, (Poly)<sub>b</sub> is a water-soluble, non-peptidic polymeric segment having from 1 to about 120 repeating units, which may be the same as or different from (Poly)<sub>a</sub>, and Y is an electrophilic or nucleophilic moiety.

17. The polymer derivative of Claim 1 having the structure Y-(Poly)<sub>b</sub>-X-(Poly)<sub>a</sub>-X-(Poly)<sub>b</sub>-Y, wherein (Poly)<sub>a</sub> is a water-soluble, non-peptidic polymeric segment having more than about 200 repeating units, X is a linking moiety that does not substantially alter the properties of the polymer derivative, (Poly)<sub>b</sub> is a water-soluble, non-peptidic polymeric segment having from 1 to about 120 repeating units, and wherein Y is an electrophilic or nucleophilic moiety.

18. The polymer of Claim 1, wherein said active moiety is selected from the group consisting of  $-(CH_2)_rCO_2H$ ,  $-(CH_2)_rCO_2NS$ ,  $-(CH_2)_rCO_2Bt$ ,  $-(CH_2)_rCH(OR)_2$ ,  $-(CH_2)_rCHO$ ,  $-(CH_2)_2-NH_2$ ,  $-(CH_2)_rM$ ,  $-(CH_2)_rS-SO_2-R$ , wherein r is 1-5, r' is 0-5, R is aryl or alkyl, NS is N-succinimidyl, Bt is 1-benzotriazolyl, and M is N-maleimidyl.

19. The polymer of Claim 1 wherein one or both of said first and second polymeric segments further comprise groups that degrade hydrolytically or enzymatically between said monomers.

20. A polymer having the composition  $\text{PEG}-[\text{X}-(\text{CH}_2\text{CH}_2\text{O})_m-\text{Y}]_q$

wherein:

PEG is a water-soluble non-peptidic polymer selected from a linear poly(ethylene glycol), alkoxy-poly(ethylene glycol), a branched poly(ethylene glycol), and a forked poly(ethylene glycol), with or without hydrolytically or enzymatically degradable linkages, where the poly(ethylene glycol) has at least 200 repeating monomer units,

X is a linking moiety,

m is from 1 to about 120,

Y is a moiety having a terminal electrophilic or nucleophilic group, and

q is from 1 to about 500.

21. The polymer of Claim 20, wherein Y is selected from the group consisting of hydroxyl, protected hydroxyl, active ester, active carbonate, acetal, aldehyde, aldehyde hydrates, alkenyl, acrylate, methacrylate, acrylamide, active sulfone, amine, protected amine, hydrazide, protected hydrazide, thiol, protected thiol, carboxylic acid, protected carboxylic acid, isocyanate, isothiocyanate, maleimide, vinylsulfone, dithiopyridine, vinylpyridine, iodoacetamide, epoxide, glyoxals, diones, mesylates, tosylates, thiosulfonate, and tresylate.

22. The polymer of Claim 20 wherein for  $q=2$ , Y is independently selected from the group consisting of hydroxyl, protected hydroxyl, active ester, active carbonate, acetal, aldehyde, aldehyde hydrates, alkenyl, acrylate, methacrylate, acrylamide, active sulfone, amine, protected amine, hydrazide, protected hydrazide, thiol, protected thiol, carboxylic acid, protected carboxylic acid, isocyanate, isothiocyanate, maleimide, vinylsulfone, dithiopyridine, vinylpyridine, iodoacetamide, epoxide, glyoxals, diones, mesylates, tosylates, thiosulfonate, and tresylate.

23. The polymer of Claim 20, wherein Y is selected from  $-(\text{CH}_2)_r\text{CO}_2\text{H}$ ,  $-(\text{CH}_2)_r\text{CO}_2\text{NS}$ ,  $-(\text{CH}_2)_r\text{CO}_2\text{Bt}$ ,  $-(\text{CH}_2)_r\text{CH}(\text{OR})_2$ ,  $-(\text{CH}_2)_r\text{CHO}$ ,  $-(\text{CH}_2)_2\text{-NH}_2$ ,  $-(\text{CH}_2)_r\text{M}$ ,

$-(CH_2)_r-S-SO_2-R$ , where  $r$  is 1-5,  $r'$  is 0-5,  $R$  is aryl or alkyl,  $NS$  is N-succinimidyl,  $Bt$  is 1-benzotriazolyl, and  $M$  is N-maleimidyl.

24. The polymer of Claim 20, wherein  $X$  is an amide or carbamate linkage.

25. The polymer of Claim 20, where the poly(ethylene glycol) has from about  
5 200 to 2000 repeating units.

26. A polymer having the composition  $R-(OCH_2CH_2)_n-X-(CH_2CH_2-O)_m-Y$   
where:

$R$  is selected from an alkyl group having from 1 to 5 carbon atoms and a functional  
moiety having a terminal electrophilic or nucleophilic group,

10  $n$  is greater than 200,

$m$  is between 1 and about 120,

$X$  is a linking moiety, and

$Y$  is a moiety having a terminal electrophilic or nucleophilic group, which may be the  
same or different from  $R$ .

15 27. A method of forming a water-soluble, non-peptidic polymer with at least  
one functional group, said method comprising the steps of:

providing a first water soluble, non-peptidic polymer composed of at least about  
200 repeating units and having at least one first functional group;

providing a second water soluble, non-peptidic polymer composed of from 1 to  
20 about 120 repeating units and having at least one of a second functional group, said  
second functional group being reactive with said first functional group of the high weight  
polymer, at least ; and wherein at least one of said first and second polymers further  
comprises a functional group that is not reactive with either of said first and second  
functional groups.

25 reacting said first and second functional groups, thereby covalently bonding said  
first and second polymers to provide a water-soluble, non-peptidic polymer with at least  
one functional group.

28. The method of Claim 27, wherein the first and second functional groups are selected from N-succinimidyl carbonate, amine, hydrazide, succinimidyl propionate and succinimidyl butanoate, succinimidyl succinate, succinimidyl ester, benzotriazole carbonate, glycidyl ether, oxycarbonylimidazole, p-nitrophenyl carbonate, aldehyde,  
5 maleimide, orthopyridyl-disulfide, acrylol, and vinylsulfone.

29. The method of Claim 27, wherein the functional group that is not reactive with the first and second functional groups is selected from the group consisting of hydroxyl, protected hydroxyl, active ester, active carbonate, acetal, aldehyde, aldehyde hydrates, alkenyl, acrylate, methacrylate, acrylamide, active sulfone, amine, protected  
10 amine, hydrazide, protected hydrazide, thiol, protected thiol, carboxylic acid, protected carboxylic acid, isocyanate, isothiocyanate, maleimide, vinylsulfone, dithiopyridine, vinylpyridine, iodoacetamide, epoxide, glyoxals, diones, mesylates, tosylates, thiosulfonate, and tresylate.

30. The method of Claim 27, wherein the first and second functional groups  
15 are reacted in the presence of a solvent selected from the group consisting of toluene, tetrahydrofuran, dioxane, acetonitrile, methylene chloride, chloroform, dimethylformamide, dimethylsulfoxide, benzene, xylene, and combinations thereof.

31. The method of Claim 27, wherein the polymers are each poly(ethylene glycol) selected from the group consisting of monofunctional and difunctional linear,  
20 branched, multiarmed, and forked forms.

32. The method of Claim 27, wherein the first polymer is a linear methoxy-poly(ethylene glycol).

33. The method of Claim 27, further comprising the step of conjugating the functional group that is not reactive to the first and second functional groups to a  
25 biologically active agent.

34. The method of Claim 33, wherein the biologically active agent is selected from a protein, peptide, carbohydrate, oligonucleotide, DNA, RNA, and lipid.

35. The method of Claim 27, wherein the first polymer comprises a protected reactive group and further including the step of removing the protecting moiety from the covalently bonded high and low weight polymers to create an additional functionality.